Letters to the Editor

Caveat Emptor

The Coronary Calcium Warranty

Min et al. (1) provide welcome evidence that coronary artery calcium (CAC) conversion from zero to a positive score occurs at low frequency before 4 years. They note that this finding applies to "middle-age, low- to intermediate-risk individuals," in whom a zero score is common. They are to be congratulated for the low dose of radiation per scan (0.5 mSV).

Although readers are cautioned that repeat CAC testing has not been formally recommended in any guideline to date, they may ask how to specifically apply these results to the population for whom current guidelines endorse baseline CAC testing (2). The mean Framingham risk score of the Min et al. (1) CAC = 0 cohort was 9%, placing many of the subjects in the low-risk group by National Cholesterol Education Program guidelines (2). CAC scoring is not currently endorsed for patients at low risk (Framingham risk score <10%), as opposed to those at intermediate risk (Framingham risk score, 10% to 20%), who may benefit from risk reclassification (2). Thus, the investigators' recommended warranty period of 4 years may be too long when applied to classically intermediate-risk patients undergoing CAC testing.

It would be beneficial for clinicians to have the "warranty period" stratified by baseline risk group (<10% and 10% to 20%). It may even be prudent to stratify further, as some have advocated for CAC testing in an expanded intermediate-risk group of 6% to 20% (e.g., <6%, 6% to 10%, and 10% to 20%) (3).

The finding that many traditional risk factors were not associated with the progression of CAC to a higher score in the baseline CAC >0 group is likely a function of the short duration of follow-up (1.9 years) and the definition of CAC progression in this group as "any increase in CAC score." Progression results in this group may have been from interscan variability alone and not from disease progression. Perhaps the investigators could have minimized the effect of variability by incorporating a more specific and clinically meaningful cutoff (such as a >15% relative change between scans [4]).

The investigators may also have been overly prudent to suggest that "caution should be applied to interpreting our results among patients who are not receiving lipid-lowering therapy." Although they express concern that the 756 patients on statin therapy (72%) may have had retarded CAC progression, randomized trials to date have not shown that statin therapy can achieve this (5–6).

CAC = 0 has enormous potential for ruling out important coronary artery disease in asymptomatic patients. The duration and application of the "warranty period" remains an important topic for further research.

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Reply

We thank Dr. McEvoy and colleagues for their interest in our study (1). They raise several pertinent points that deserve response. As noted, the mean 10-year coronary heart disease (CHD) Framingham risk score for our study cohort with coronary artery calcium (CAC) scores of zero was 9%, which comprised 62% low-risk (<10% 10-year risk), 34% intermediate-risk (10% to 20% 10-year risk), and 5% high-risk (>20% 10-year risk) patients. Although CAC scoring is not presently endorsed for low-risk patients, we observed relationships of CAC conversion and time to conversion in low-risk versus intermediate-risk patients that merit consideration.

Time to conversion to CAC >0 in low-risk patients did not differ compared with intermediate-risk patients (4.01 vs. 4.17 years, p = 0.99), and low-risk patients even trended toward higher rates of conversion from CAC = 0 to CAC >0 (11% vs. 8%, p = 0.08). These findings are in keeping with recent population-based studies of CAC, including the Multiethnic Study of Atherosclerosis, which demonstrated a prognostic value of CAC beyond the

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Framingham risk score across age, sex, and ethnic category, and the Dallas Heart Study, in which CAC scores >100 were observed in a substantial proportion of low-risk patients who would not otherwise have been candidates for statin-based therapy (2,3). Given the uneasiness on the part of many clinicians about relying solely on the Framingham risk score (particularly in younger women and men and those with strong family histories of premature CHD), the performance of CAC scoring in low-risk patients may represent not only a clinical reality but also an opportunity for improved stratification and reclassification of CHD risk.

Dr. McEvoy and colleagues also suggest that progression of CAC >0 to a higher CAC score may be due to the intermediate follow-up period of 1.9 years or interscan variability. Using the "clinically meaningful cutoff" of a >15% increase between CAC scans they recommend, the relationship of increase in CAC remains dependent solely on the baseline CAC score. In stepwise multivariate analyses, CAC >400 and CAC >600 were the only predictive factors for CAC rise in both low-risk (hazard ratio: 2.08; 95% confidence interval: 1.29 to 3.35; p = 0.003) and intermediate-risk (hazard ratio: 1.82; 95% confidence interval: 1.23 to 2.58; p = 0.001) patients.

We agree with Dr. McEvoy and colleagues that many questions related to the potential effects of lipid-lowering therapies on CAC remain unanswered, and we agree that CAC = 0 holds great potential for optimizing the classification of asymptomatic patients. We hope that our findings that demonstrate a 4-year "warranty period" of CAC = 0 across all strata of CHD risk will add to the foundation of scientific evidence on which future studies can be based, and in the interim, may inform physicians who use CAC scanning that retesting patients at intervals of <4 years is unlikely to be helpful.

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Timing of Intervention in Patients Undergoing Invasive Management for Acute Coronary Syndromes

With interest we read the recent report by Sorajja et al. (1), showing that delaying revascularization with percutaneous coronary intervention (PCI) for >24 h in patients with acute coronary syndrome was associated with an increased hazard for mortality and adverse ischemic outcomes, when compared with intervention within 8 h or 8 to 24 h (1).

This finding was mainly driven by significantly more myocardial infarctions (MI) occurring in the delayed intervention group (>24 h). Because of the natural course of cardiac biomarkers in the setting of myocardial ischemia, procedure-related myonecrosis with immediate intervention is difficult to discern from elevated biomarker levels before PCI due to the index event. Thus, the diagnosis of procedure-related MI in early PCI is prone to detection bias.

Furthermore, the study had made a rather firm selection of patients, because 4,491 patients who did not undergo PCI after diagnostic angiography were left out. We hypothesize that patients with mild coronary artery disease underwent early PCI influenced by the recent symptoms associated with the index event, whereas stabilized patients with mild CAD undergoing delayed angiography did not undergo PCI and were excluded from the analysis. The authors should have at least reported outcomes by timing of angiography.

Finally, the Kaplan-Meier curves for mortality or MI continue to diverge up to 30 days and thereafter. Apparently, the risk of delaying intervention is not limited to an excess risk during the waiting period, but also extends to the period after the intervention. This observation is suggestive of patient selection for late PCI rather than of an implicit higher risk of the intervention being performed at a later time point. This observation of selection bias is corroborated by the observation that patients who received PCI >24 h had a worse baseline-risk profile and angiographic characteristics. We note that the authors did not explain the higher death or MI hazard with delayed intervention.

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